

1,169,945



PATENT SPECIFICATION

NO DRAWINGS

1,169,945

Inventor: GERAINT JONES

Date of filing Complete Specification: 11 July, 1967.

Date of Application (No. 38196/66): 25 Aug., 1966.

Complete Specification Published: 5 Nov., 1969.

Index at acceptance: —A5 B(38Y, 383, 43Y, 431, 58Y, 586, 64Y, 641)

International Classification: —A 61 k 27/00

COMPLETE SPECIFICATION

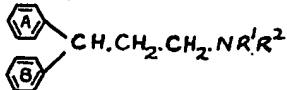
Pharmaceutical Compositions containing Diphenylalkyl-amine Derivatives

We, ED GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE, a body corporate organised and existing under the laws of Switzerland, of 6110, Wohlhusen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to new pharmaceutical compositions having antidepressant activity.

Certain 3,3-diphenylpropylamine derivatives are known compounds, but it was not known heretofore that compounds of this type were useful as antidepressants. We have now made the unexpected discovery that compounds of this type have antidepressant activity, and therein lies the basis of this invention.

20 According to the invention we provide pharmaceutical compositions comprising at least one alkane derivative of the formula:—



25 wherein R¹ stands for hydrogen or an alkyl radical, R² stands for an alkyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, and a pharmaceutically-acceptable diluent or carrier.

30 As a suitable value for R², or for R¹ when it stands for an alkyl radical, there may be mentioned, for example, an alkyl radical of not more than 6 carbon atoms and more particularly an alkyl radical of not more than 2

carbon atoms, for example the methyl or ethyl radical.

The substituent(s) which may optionally be present in either or both of the phenyl radicals A and B may, for example, be selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkoxy and alkyl radicals of not more than 3 carbon atoms, for example the methoxy or methyl radical.

40 A preferred group of active ingredients consists of alkane derivatives of the above formula wherein R¹ stands for hydrogen or the methyl radical, R² stands for the methyl or ethyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and the trifluoromethyl radical.

45 As alkane derivatives which may be used as active ingredients in the pharmaceutical compositions of the invention there may be mentioned, for example, the known compounds N,N - dimethyl - 3,3 - diphenylpropylamine, and N - methyl - 3,3 - diphenylpropylamine, and N - ethyl - N - methyl - 3,3 - diphenylpropylamine, and the new compounds: N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2-methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - chlorophenyl)propylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - fluorophenyl)propylamine, N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

50

55

60

65

70

75

80

[Price 4s. 6d.]

As suitable acid-addition salts there may be mentioned salts derived from inorganic or organic acids affording pharmaceutically-acceptable anions, for example hydrochlorides, oxalates, citrates, maleates or tartrates.

Suitable pharmaceutically-acceptable diluents or carriers for use as excipients in the compositions of the invention are those known to the art and used in the preparation of pharmaceutical formulations for human and veterinary medication.

The pharmaceutical compositions of the invention include compositions which are suitable for oral administration. These include, for example, solid compositions, for example tablets, pills, capsules, dispersible powders and granules, which may optionally be coated, for example with a sweetening agent and/or a protective material designed to modify the distribution and absorption of the active ingredient or ingredients in the digestive tract. They also include orally-administerable semi-solid or liquid formations, for example pharmaceutically-acceptable emulsions, syrups, dispersions and solutions, either for administration *per se* with or without flavouring agents or after confinement in some suitable way, for example in capsules.

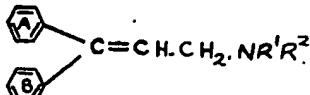
The pharmaceutical compositions of the invention also include liquid compositions which are sterile aqueous solutions, suspensions or emulsions, or sterile non-aqueous solutions or suspensions which can be administered by injection, for example intravenously, subcutaneously or intramuscularly. Those injectable compositions of the invention which are suspensions contain their particulate matter in a finely divided form, for example in a micro-pulverised form, and those compositions which are aqueous suspensions may optionally contain small amounts of such agents as are commonly used to facilitate the manufacture and maintain the efficacy of aqueous suspensions, for example dispersing and suspending agents.

Suitable vehicles for the non-aqueous solutions and suspensions of the invention include, for example, water-miscible non-toxic vehicles, for example propylene glycol and polyethylene glycol, and water-immiscible non-toxic vehicles, for example injectable vegetable oils, for example arachis oil, and oil-like injectable organic esters, for example dibutyl succinate. The said water-immiscible vehicles may also contain metallic soaps, for example aluminium stearate.

The sterile injectable solutions, suspensions or emulsions of the invention may be obtained sterile by known procedures, for example by aseptic formulation, by Seitz filtration, by irradiation, by the incorporation of sterilising agents in the compositions, or by heat treatment.

The compositions of the invention include pharmaceutical compositions which are sterile powders comprising the active ingredient or ingredients together with such non-toxic pharmaceutical excipients as are required to provide, on mixing with water, sterile aqueous solutions or suspensions suitable for parenteral administration.

The alkane derivatives which are used as the active ingredients in the pharmaceutical compositions of this invention may be obtained by the reduction of an alkene derivative of the formula:—



wherein A, B, R¹ and R² have the meanings stated above, or an acid-addition salt thereof, as described in our co-pending patent application No. 38195/66 (Serial No. 1,169,944) of even date herewith, or by analogous means.

The invention is illustrated but not limited by the following Example in which the parts are by weight:—

EXAMPLE

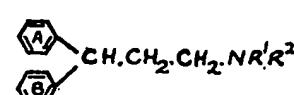
A mixture of 25 parts of N,N - dimethyl-3,3 - diphenylpropylamine hydrochloride, 125 parts of maize starch, 270 parts of calcium phosphate and 1 part of magnesium stearate is compressed, and the compressed material is then broken down into granules by passage through a 16-mesh screen. The granules so obtained are then compressed into tablets which are suitable for oral administration for therapeutic purposes.

In place of the 25 parts of N,N - dimethyl-3,3 - diphenylpropylamine hydrochloride used in the above example there may be used 25 parts of any of the following compounds:—

N - methyl - 3,3 - diphenylpropylamine hydrochloride, N - ethyl - 3,3 - diphenylpropylamine hydrochloride or N - ethyl - N - methyl - 3,3 - diphenylpropylamine hydrochloride. It is to be understood that the pharmaceutical compositions claimed in the following claims do not include simple solutions of the alkane derivatives(s) in question in common solvents for example water.

Subject to this disclaimer, WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising at least one alkane derivative of the formula:—



wherein R¹ stands for hydrogen or an alkyl radical, R² stands for an alkyl radical, and either or both of the phenyl radicals A and B

BEST AVAILABLE COPY

1,169,945

3

5 may optionally be substituted with one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, and a pharmaceutically-acceptable diluent or carrier.

10 2. A composition as claimed in claim 1 wherein R¹ stands for hydrogen or an alkyl radical of not more than 6 carbon atoms, R² stands for an alkyl radical of not more than 6 carbon atoms, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from fluorine and chlorine atoms, the trifluoromethyl radicals, and alkyl and alkoxy radicals of not more than 3 carbon atoms.

15 3. A composition as claimed in claim 1 wherein R¹ stands for hydrogen or the methyl radical, R² stands for the methyl or ethyl radical, and either or both of the phenyl radicals A and B may optionally be substituted with one or two substituents selected from halogen atoms and the trifluoromethyl radical.

20 4. A composition as claimed in claim 3 wherein the halogen substituent(s) is or are selected from fluorine and chlorine atoms.

25 5. A composition as claimed in claim 1 in which the active ingredient is N,N - dimethyl-3,3 - diphenylpropylamine or an acid-addition salt thereof.

30 6. A composition as claimed in claim 1 in which the active ingredient(s) is or are selected from N - methyl - 3,3 - diphenylpropylamine,

N - ethyl - N - methyl - 3,3 - diphenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - fluoro-phenyl)propylamine, N,N - dimethyl - 3 - (4 - fluoro-phenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluoro-phenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - chlorophenyl)propylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - (3 - fluoro-phenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3,3 - bis - (3 - fluoro-phenyl)propylamine, N - methyl - 3,3 - bis - (4 - fluoro-phenyl)propylamine, N,N - dimethyl-3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

7. A composition as claimed in any of claims 1 to 6 which is in the form of a tablet, pill, capsule, dispersible powder or granule, emulsion, syrup, dispersion, non-sterile solution, or a sterile injectable aqueous solution, suspension or emulsion or a sterile injectable non-aqueous solution or suspension, or a sterile powder.

8. A tablet, claimed in claim 7, substantially as described in the foregoing Example.

WALTER SCOTT,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.